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TELL-TALE MARKER SPOTS EXPIRED VACCINES

by Bob Stanley

OTTAWA, IDRC -- An unusual example of collaboration between public and private enterprise in several countries has led to the development of a simple device that could save the lives of hundreds of thousands of children in the developing world.

The device is a little red sticker that turns first brown, and then black when it gets hot. It is an elegantly simple solution to a problem that has been limiting the success of mass-immunization programs in the tropics. Vaccines against common childhood diseases are extremely sensitive to heat: the higher the temperature, the shorter their effective life.

A vial of measles vaccine, for example, is good for 54 days at a temperature of 25 degrees Celsius. At 37°C its life is reduced to 12 days at most. But there is no visible sign of deterioration, no way in which the health worker administering the vaccine can detect the fact that it has expired. Polio vaccines deteriorate in a similar fashion.

This characteristic presents no real problem in an industrialized country, where refrigeration is readily available, and vaccines become part of a "cold chain" process from manufacture to vaccination. But in rural areas of developing countries the cold chain quickly breaks down when the health worker must travel from village to village, often spending days at a time away from the clinic or health centre.

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The World Health Organization's Expanded Programme for Immunization (WHO/EPI) states bluntly: "The biggest stumbling blocks to successful immunization programmes are not medical or technical, but the practical difficulties arising from field operations.... keeping vaccines safe and effective from manufacture to child."

No-one knows for sure just how many children receive useless measles vaccinations each year, but estimates vary between 10 million and 16 million. Given an estimated mortality rate from measles in the tropics of 10 percent, and assuming that 30 percent of unprotected children contract the disease, that means at least 300,000 potential child deaths annually, even using the most conservative figure, according to Dr Patrick Tam, program officer for the Program for Appropriate Technology in Health (PATH).

Dr Tam, a bio-engineer, is responsible for coordinating the development of the little red sticker that promises to solve this problem. The sticker's active ingredient is a chemical called 2,4-hexadiyne-1,6-(p-toluenesulfonate), more conveniently known as PTS. Exposure to heat causes PTS to polymerize -- a shifting of molecules that results in its changing colour. The higher the temperature, the more rapid the change.

The sticker is called a time-temperature indicator. It was devised initially by the Allied Corporation in the US. But Allied estimated it would cost them from US$4 million to US$5 million to develop the indicator for mass-production, and that they would be unable to recover their investment. So Allied approached WHO with their invention -- and that was when PATH heard about it.

The small, Seattle-based non-profit agency has very little cash, but it has a good reputation, and excellent contacts. In short order, Dr Tam developed a proposal for a one-year feasibility study of Allied's prototype indicator, and obtained 95 percent of the funding needed from the Edna McConnell Clark Foundation, of New York, and Canada's International Development Research Centre

(IDRC). The total cost of this study was just Cdn$168,900.

One of the first questions to be resolved was the safety of the product, both for health workers in the field and for those involved in the production process. Toxicology studies showed possible harmful effects from contact with PTS. To overcome this problem, a clear plastic coating was developed to prevent direct contact with the chemical, and production workers were instructed to wear protective gloves and masks.

With safety assured, the PATH researchers began detailed testing. They found that the indicators could be manufactured to closely parallel the rate of degradation of measles vaccines obtained from major manufacturers, and that they could be manufactured to match the WHO/EPI recommended standard of seven days maximum exposure at 37°C. Working closely with the staff of WHO/EPI, the researchers used this same technology to develop a "management indicator". This is a label for use on large batches of vaccine. It incorporates four PTS dots that change colour in sequence according to the extent of exposure the carton containing the vaccine vials has undergone. Thus managers can see at a glance which batches must be used first, or have already expired. The label also has space for a complete shipping history of each carton.

The single-vial indicators are attached to the tops of vials so that health workers cannot fail to notice if the red colour has changed to brownish-black. Successful preliminary field tests were carried out in Mexico, the Philippines, and Indonesia. Connaught Laboratories, of Toronto, who are collaborating with PATH on the adaptation of the indicator for use with polio vaccines, carried out additional field tests in Pakistan at their own expense. More tests are also being conducted in the People's Republic of China after the Chinese government requested a batch of the prototype indicators for testing with their locally manufactured vaccines.

The second phase of the project, now nearing completion, cost a further Cdn$268,000, provided by the two original donors plus Oxfam of the United

Kingdom, and also involves another Canadian vaccine manufacturer, the Institut Armand Frappier. More extensive field testing is being carried out in 11 countries of Africa, Asia and Latin America in this phase with additional funding from WHO/EPI. The tests involve evaluation by health workers and others of the design of the indicators and the instructional materials that have been prepared for use with them. The exercise will also help to introduce the concept of visual indicators into many ministries of health. PATH is collaborating closely at this stage with WHO/EPI and other major agencies, such as UNICEF, to ensure successful introduction of the indicators as soon as they become available.

The technical problems to be overcome in order to bring the indicators to mass-production are considerable, but not insurmountable according to Dr Tam. And mass-production is essential, he says, to keep the eventual cost of the indicators as low as possible.

The PTS compound is to be formulated into an ink suitable for printing presses, and there is machinery to be developed for mass application of the indicators on individual vials and on shipping cartons. There are manuals to be prepared as a first step to the transfer of the technology. And finally there is an agreement on royalties to be finalized with ACC, who still hold the patent on the invention until the early 1990s.

If all continues to go well, mass-production could begin as early as 1983, says Dr Tam, and health workers around the world will soon become accustomed to looking for that little red sticker that will tell them that <u>this</u> vaccination will give a child protection.

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